EXHIBIT H

GOODMAN & GILMAN'S The PHARMACOLOGICAL BASIS OF THERAPEUTICS

Ninth Edition

McGraw-Hill
HEALTH PROFESSIONS DIVISION

New York St. Louis San Francisco Auckland Bogotá Caracas Lisbon London Madrid
Mexico City Milan Montreal New Delhi San Juan Singapore Sydney Tokyo Toronto

ject insulin into their thigh may experience a precipitous drop in blood sugar that is not seen following injection into the arm or abdominal wall, since running markedly increases blood flow to the leg. Generally, the rate of absorption following injection of an aqueous preparation into the deltoid or vastus lateralis is faster than when the injection is made into the gluteus maximus. The rate is particularly slower for females after injection into the gluteus maximus. This has been attributed to the different distribution of subcutaneous fat in males and females, since fat is relatively poorly perfused. Very obese or emaciated patients may exhibit unusual patterns of absorption following intramuscular or subcutaneous injection. Very slow, constant absorption from the intramuscular site results if the drug is injected in solution in oil or suspended in various other repository vehicles. Penicillin often is administered in this manner. Substances too irritating to be injected subcutaneously may sometimes be given intramuscularly.

Intraarterial. Occasionally a drug is injected directly into an artery to localize its effect in a particular tissue or organ. However, this practice usually has dubious therapeutic value. Diagnostic agents are sometimes administered by this route. Intraarterial injection requires great care and should be reserved for experts. The first-pass and cleansing effects of the lung are not available when drugs are given by this route.

Intrathecal. The blood–brain barrier and the blood–cerebrospinal fluid barrier often preclude or slow the entrance of drugs into the CNS. Therefore, when local and rapid effects of drugs on the meninges or cerebrospinal axis are desired, as in spinal anesthesia or acute CNS infections, drugs are sometimes injected directly into the spinal subarachnoid space.

Intraperitoneal. The peritoneal cavity offers a large absorbing surface from which drugs enter the circulation rapidly, but primarily by way of the portal vein; first-pass hepatic losses are thus possible. Intraperitoneal injection is a common laboratory procedure, but it is seldom employed clinically. The dangers of producing infection and adhesions are too great to warrant the routine use of this route in human beings.

Pulmonary Absorption. Gaseous and volatile drugs may be inhaled and absorbed through the pulmonary epithelium and mucous membranes of the respiratory tract. Access to the circulation is rapid by this route, because the surface area is large. The principles governing absorption and excretion of anesthetic and other therapeutic gases are discussed in Chapters 13, 14, and 16.

In addition, solutions of drugs can be atomized and the fine droplets in air (aerosol) inhaled. Advantages are the almost instantaneous absorption of a drug into the blood, avoidance of hepatic first-pass loss, and, in the case of pulmonary disease, local application of the drug at the desired site of action. For example, drugs can be given in this manner for the treatment of bronchial asthma (*see* Chapter 28). The main disadvantages are poor ability to regulate the dose, cumbersomeness of the methods of administration, and the fact that many gaseous and volatile drugs produce irritation of the pulmonary epithelium.

Pulmonary absorption is an important route of entry of certain drugs of abuse and of toxic environmental substances of varied composition and physical states (*see* Section XVII). Both local and systemic reactions to allergens may occur subsequent to inhalation.

Topical Application. ***Mucous Membranes.*** Drugs are applied to the mucous membranes of the conjunctiva, nasopharynx, oropharynx, vagina, colon, urethra, and urinary bladder primarily for their local effects. Occasionally, as in the application of antidiuretic hormone to the nasal mucosa, systemic absorption is the goal. Absorption through mucous membranes occurs readily. In fact, local anesthetics applied for local effect sometimes may be absorbed so rapidly that they produce systemic toxicity.

Skin. Few drugs readily penetrate the intact skin. Absorption of those that do is proportional to the surface area over which they are applied and to their lipid solubility, since the epidermis behaves as a lipid barrier (*see* Chapter 64). The dermis, however, is freely permeable to many solutes; consequently, systemic absorption of drugs occurs much more readily through abraded, burned, or denuded skin. Inflammation and other conditions that increase cutaneous blood flow also enhance absorption. Toxic effects sometimes are produced by absorption through the skin of highly lipid-soluble substances (*e.g.*, a lipid-soluble insecticide in an organic solvent). Absorption through the skin can be enhanced by suspending the drug in an oily vehicle and rubbing the resulting preparation into the skin. This method of administration is known as *inunction*. Because hydrated skin is more permeable than dry skin, the dosage form may be modified or an occlusive dressing may be used to facilitate absorption. Controlled-release topical patches are recent innovations. A patch containing scopolamine, placed behind the ear where body temperature and blood flow enhance absorption, releases sufficient drug to the systemic circulation to protect the wearer from motion sickness. Transdermal estrogen replacement therapy yields low maintenance levels of estradiol while minimizing the high estrone metabolite levels observed following oral administration.

Eye. Topically applied ophthalmic drugs are used primarily for their local effects (*see* Chapter 65). Systemic absorption that results from drainage through the nasolacrimal canal is usually undesirable. In addition, drug that is absorbed after such drainage is not subject to first-pass hepatic elimination. Unwanted systemic pharmacological effects may occur for this reason when β-adrenergic antagonists are administered as ophthalmic drops. Local effects usually require absorption of the drug through the cornea; corneal infection or trauma may thus result in more rapid absorption. Ophthalmic delivery systems that provide prolonged duration of action (*e.g.*, suspensions and ointments) are useful additions to ophthalmic therapy. Ocular inserts, developed more recently, provide continuous delivery of low amounts of drug. Very little is lost through drainage; hence, systemic side effects are minimized.

Bioequivalence. Drug products are considered to be pharmaceutical equivalents if they contain the same active ingredients and are identical in strength or concentration, dosage form, and route of administration. Two pharmaceutically equivalent drug products are considered to be bioequivalent when the rates and extents of bioavailability of the active ingredient in the two products are not significantly different under suitable test conditions. In the past, dosage forms of a drug from different manufacturers and even different lots of preparations from a single manufacturer sometimes differed in their bioavailability. Such differences were seen primarily among oral dosage forms of poorly soluble, slowly absorbed drugs. They result from differences in crystal form, particle size, or other physical characteristics of the drug that are not rigidly controlled in formulation

and manufacture of the preparations. These factors affect disintegration of the dosage form and dissolution of the drug and hence the rate and extent of drug absorption.

The potential nonequivalence of different drug preparations has been a matter of concern. Strengthened regulatory requirements have resulted in few, if any, documented cases of nonequivalence between approved drug products. The significance of possible nonequivalence of drug preparations is further discussed in connection with drug nomenclature and the choice of drug name in writing prescription orders (*see* Appendix I).

DISTRIBUTION OF DRUGS

After a drug is absorbed or injected into the bloodstream, it may be distributed into interstitial and cellular fluids. Patterns of drug distribution reflect certain physiological factors and physicochemical properties of drugs. An initial phase of distribution may be distinguished that reflects cardiac output and regional blood flow. Heart, liver, kidney, brain, and other well-perfused organs receive most of the drug during the first few minutes after absorption. Delivery of drug to muscle, most viscera, skin, and fat is slower, and these tissues may require several minutes to several hours before steady state is attained. A second phase of drug distribution may therefore be distinguished; this is also limited by blood flow, and it involves a far larger fraction of the body mass than does the first phase. Superimposed on patterns of distribution of blood flow are factors that determine the rate at which drugs diffuse into tissues. Diffusion into the interstitial compartment occurs rapidly because of the highly permeable nature of capillary endothelial membranes (except in the brain). Lipid-insoluble drugs that permeate membranes poorly are restricted in their distribution and hence in their potential sites of action. Distribution also may be limited by drug binding to plasma proteins, particularly albumin for acidic drugs and α_1-acid glycoprotein for basic drugs. An agent that is extensively and strongly bound has limited access to cellular sites of action, and it may be metabolized and eliminated slowly. Drugs may accumulate in tissues in higher concentrations than would be expected from diffusion equilibria as a result of pH gradients, binding to intracellular constituents, or partitioning into lipid.

Drug that has accumulated in a given tissue may serve as a reservoir that prolongs drug action in that same tissue or at a distant site reached through the circulation. An example that illustrates many of these factors is the use of the intravenous anesthetic thiopental, a highly lipid-soluble drug. Because blood flow to the brain is so high, the drug reaches its maximal concentration in brain within a minute after it is injected intravenously. After injection is concluded, the plasma concentration falls as thiopental diffuses into other tissues, such as muscle. The concentration of the drug in brain follows that of the plasma, because there is little binding of the drug to brain constituents. Thus, onset of anesthesia is rapid, but so is its termination. Both are directly related to the concentration of drug in the brain. A third phase of distribution for this drug is due to the slow, blood-flow–limited uptake by fat. With administration of successive doses of thiopental, accumulation of drug takes place in fat and other tissues that can store large amounts of the compound. These can become reservoirs for the maintenance of the plasma concentration, and therefore the brain concentration, at or above the threshold required for anesthesia. Thus, a drug that is short acting because of rapid redistribution to sites at which the agent has no pharmacological action can become long acting when these storage sites are "filled" and termination of the drug's action becomes dependent on biotransformation and excretion (*see* Benet, 1978).

Since the difference in pH between intracellular and extracellular fluids is small (7.0 vs. 7.4), this factor can result in only a relatively small concentration gradient of drug across the plasma membrane. Weak bases are slightly concentrated inside of cells, while the concentration of weak acids is slightly lower in the cells than in extracellular fluids. Lowering the pH of extracellular fluid increases the intracellular concentration of weak acids and decreases that of weak bases, provided that the intracellular pH does not also change and that the pH change does not simultaneously affect the binding, biotransformation, or excretion of the drug. Elevating the pH produces the opposite effects (*see* Figure 1–2).

Central Nervous System and Cerebrospinal Fluid. The distribution of drugs to the CNS from the bloodstream is unique, mainly in that entry of drugs into the cerebrospinal fluid and extracellular space of the CNS is restricted. The restriction is similar to that across the gastrointestinal epithelium. Endothelial cells of the brain capillaries differ from their counterparts in most tissues by the absence of intercellular pores and pinocytotic vesicles. Tight junctions predominate, and aqueous bulk flow thus is severely restricted. This is not unique to the CNS capillaries (tight junctions appear in many muscle capillaries as well). It is likely that the unique arrangement of pericapillary glial cells also contributes to the slow diffusion of organic acids and bases into the CNS. The drug molecules probably must traverse not only endothelial but also perivascular cell membranes before reaching neurons or other target cells in the CNS. Cerebral blood flow is the only limitation to permeation of the CNS by highly lipid-soluble drugs. The rate of diffusion of drugs with increas-

Remington's Pharmaceutical Sciences

100 YEARS

consistent, and the presence of food may enhance or diminish the absorption of drugs. The most common type of interaction occurs when a food constituent binds the drug and the food-drug complex cannot pass through the gut wall. For example, complexation of tetracycline antibiotics may occur when these drugs are administered with dairy products or with antacids containing aluminum, calcium, or magnesium. The presence of a large meal in the stomach will delay gastric emptying. If a drug that is absorbed in the intestine is ingested with a large meal, the delay in gastric emptying may result in a delay in absorption of the drug. However, the presence of food in the stomach has also been shown to *increase* absorption of some drugs. For example, the bioavailabilities of the β-adrenergic blocking drugs, propranolol and metoprolol, are enhanced by the presence of food.[3] Therefore, because of the difficulty in predicting the absorption pattern of a drug in the presence of food, it is usually advisable to administer drugs when the stomach is empty. An exception to this advice is with drugs which cause gastrointestinal irritation and nausea. These drugs must be given with food to prevent these side effects. It is recommended that such drugs *always* be taken with food to compensate for the differences in absorption that might occur if they were given one time with food and another time without food.

Water taken concomitantly with certain drugs may increase bioavailability. The administration of aspirin, erythromycin stearate, amoxicillin or theophylline with 250 mL of water results in greater bioavailability than if the same drugs are ingested with only 25 mL of water.[4] It is probable that the increased amount of water enhances the amount of drug absorbed by improving drug dissolution as well as by hastening gastric emptying.

Diseases that affect the structure and function of the gastrointestinal tract are also capable of altering the absorption of drugs after oral administration. However, no consistent pattern develops; rather, there appears to be a complex relationship between the effect of the disease on stomach and intestinal functions and the absorption of the drug in question. For example, diseases such as diabetes mellitus or chronic renal failure, diseases that delay gastric emptying, will markedly delay the absorption and onset of effect of drugs that must reach the small intestine before they are absorbed. This has been a problem with the use of phenytoin in patients with chronic renal failure. Celiac disease and Crohn's disease, two diseases that alter the intestinal epithelium, have been studied in detail.[5] In these diseases, absorption of some drugs is greatly affected, but there is no consistent pattern of altered drug absorption.

When a drug is to be administered orally to a patient with altered gastrointestinal motility, diseases of the stomach and small or large intestine, previous stomach or intestinal surgery, or gastrointestinal infection, there is a considerable probability that drug absorption characteristics in these patients will differ from those in healthy volunteers. This may result in a change in the time of peak blood level or the extent of absorption. It is advisable to observe such patients closely for clinical effect during initial drug administration and during chronic dosing in order to assess the influence of alterations in absorption and to correct dosing regimens accordingly. The monitoring of drug blood concentrations may be beneficial in adjusting dose.

Non-Oral Routes—Drugs are administered by a variety of non-oral routes. These include: subcutaneous, intramuscular, intravenous, inhalation, percutaneous, buccal, sublingual, rectal, vaginal, intra-arterial and intrathecal. In the cases of inhalation, topical application to the skin or mucous membranes, rectal, vaginal, intra-arterial or intrathecal administration, the route is often chosen to ensure that drugs reach a specific site with a minimum of systemic absorption. The rationale is that the maximum concentration of drug will be at the site of action so that side effects will be lessened. Nevertheless, if large doses are administered by these routes, enough drug may reach the general circulation to produce side effects. Therefore, the dose and preparation should be such that limited quantities of drug reach the systemic circulation. The beta-adrenergic agonists, metaproterenol and albuterol, when administered by inhalation produce bronchodilatation at doses that avoid serious systemic side effects. Similarly, the corticosteroid, beclomethasone, can also be administered by this route for the management of chronic asthma. Low doses of beclomethasone by inhalation are without the serious systemic side effects of oral steroids. However, as the dose is increased beyond two inhalations four times a day, for an average daily dose of 400 μg, there is a greater incidence of side effects, including adrenal suppression.

The *topical* administration of drugs is rapidly becoming an important route of drug administration of systemic drugs. Previously used only for the application of drugs for local effects in diseases of the skin, it is now being explored as a means of administering drugs for their systemic effects. Nitroglycerin is commonly applied to the skin in the form of an ointment or transdermal patches; it is rapidly absorbed and provides sustained blood levels. Sublingual nitroglycerin is also employed to produce therapeutic blood levels; it produces a maximal effect on anginal pain within 3 to 5 mins but lasts only 20 to 60 min. In contrast, nitroglycerin ointment provides peak blood concentrations in about one hour and the effect on anginal pain may last for several hours. The sublingual tablets should be used to suppress acute angina attacks, whereas nitroglycerin ointment or transdermal patches may be useful to prevent recurrence of episodes of angina for prolonged periods, such as during the night. Whether or not the continuous administration of nitrates by this route will result in the development of tolerance is not clear at this time. There are several other drugs, such as those used to treat hypertension, for which percutaneous administration is being investigated as a means of attaining sustained plasma levels.

Close *intra-arterial* administration of drugs is used to get drugs directly to a target site or organ in high concentration. After it has passed through the target region it is distributed in the entire blood volume, which reduces the systemic levels of the drug and the consequent side effects. One example of this mode of drug administration is the use of cytotoxic drugs for the treatment of primary or metastatic tumors of liver. The infusion of drugs into the hepatic artery exposes the tumor to higher drug concentrations than can be tolerated with intravenous administration. If the drug is efficiently extracted by liver, the exposure of sensitive tissues such as bone marrow and gastrointestinal epithelium to the drug will be decreased. For example, after hepatic artery infusion of floxuridine (FUDR) hepatic vein concentrations are 2 to 6 times higher than comparable drug concentrations following intravenous infusion yet systemic blood concentrations are 75% less. Thus, the therapeutic index of FUDR in the treatment of liver cancer is considerably increased by hepatic arterial infusion. This type of selective drug administration may be beneficial with other drugs that have low therapeutic indices.

Intrathecal injection is used to deliver drugs to the brain in sufficient concentration to produce an effect but at the same time to reduce the incidence or severity of systemic side effects. The intrathecal administration of the cancer chemotherapeutic agent, methotrexate, is frequently employed in the management of leukemic involvement of the central nervous system. The epidural administration of morphine, which produces long-lasting (6–30 hrs) analgesia with minimal side effects, is proving to be of benefit in the management of chronic pain.

Remington: The Science and Practice of Pharmacy . . . *A treatise on the theory and practice of the pharmaceutical sciences, with essential information about pharmaceutical and medicinal agents; also, a guide to the professional responsibilities of the pharmacist as the drug information specialist of the health team . . . A textbook and reference work for pharmacists, physicians, and other practitioners of the pharmaceutical and medical sciences.*

AUTHORS

The 133 chapters of this edition of *Remington* were written by the editors, by members of the Editorial Board, and by the authors listed on pages xi to xv.

Director

Philip P Gerbino 1995-2005

Twenty-first Edition—2005

Published in the 185th year of the
PHILADELPHIA COLLEGE OF PHARMACY AND SCIENCE

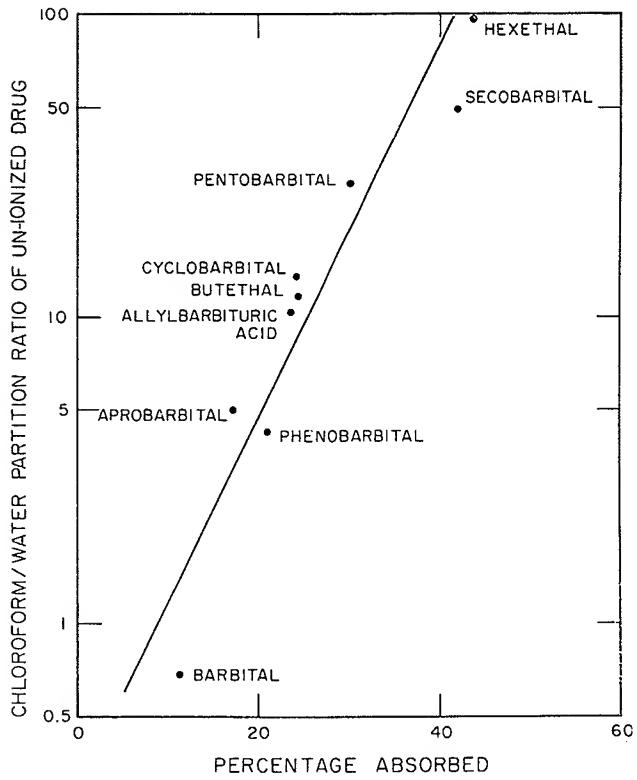

Figure 57-11. The relationship of absorption of the un-ionized forms of drugs from the colon of the rat to the chloroform:water partition coefficient. (From Schanker LS. *Adv Drug Res* 1964; 1:71.)

the pH of gastric fluid. Nevertheless, when a drug is a weak acid or base, the un-ionized form, with a favorable partition coefficient, passes through a biological membrane so much more readily than the ionized form that for all practical purposes, only the un-ionized form is said to pass through the membrane. This has become known as the *principle of nonionic diffusion.*

This principle is the reason that only the concentrations of the un-ionized form of the barbiturates are plotted in Figure 57-11.

For the purpose of further illustrating the principle, Table 57-1 is provided.[7] In the table, the permeability constants for penetration into the cerebral spinal fluid of rats are higher for un-ionized drugs than for ionized ones. The apparent exceptions—barbital, sulfaguanidine, and acetylaminoantipyr may be explained by the dipolarity of the un-ionized mole With barbital, the two lipophilic ethyl groups are too sm compensate for the considerable dipolarity of the un-io barbituric acid ring; also it may be seen that barbital is a ciably ionized, which contributes to the relatively small pe ability constant. Sulfaguanidine and acetylaminoantip are both very polar molecules. Mecamylamine also mig considered an exception, since it shows a modest permeal even though strongly ionized; there is no dipolarity in mec lamine except in the amino group.

Absorption of Drugs

Absorption is the process of movement of a drug from the s application into the extracellular compartment of the body much as there is a great similarity among the various membr that a drug may pass through to gain access to the extracel fluid, it might be expected that the particular site of applic (or *route*) would make little difference to the successful ab tion of the drug. In actual fact, it makes a great deal of differ many factors, other than the structure and composition o membrane, determine the ease with which a drug is abso These factors are discussed in the following sections, along an account of the ways that drug formulations may be ma lated to alter the ability of a drug to be absorbed readily.

ROUTES OF ADMINISTRATION

Drugs may be administered by many different routes. The ious routes include oral, rectal, sublingual or buccal, enteral, inhalation, and topical. The choice of a route dep upon both convenience and necessity.

ORAL ROUTE—This is obviously the most conve route for access to the systemic circulation, providing various factors do not militate against this route. Oral ad istration does not always give rise to sufficiently high pla concentrations to be effective; some drugs are absorbed u dictably or erratically; patients occasionally have an abso malfunction. Drugs may not be given by mouth to patients GI intolerance or who are in preparation for anesthesia o have had GI surgery. Oral administration also is precl in coma.

RECTAL ROUTE—Drugs that ordinarily are adm tered by the oral route usually can be administered by inje

Table 57-1. Rates of Entry of Drugs in CSF and the Degrees of Ionization of Drugs at pH 7.4[7]

DRUG/CHEMICAL	% BINDING TO PLASMA PROTEIN	pK_a[a]	% UN-IONIZED AT pH 7.4	PERMEABILITY CO (P min^{-1}) ± S.E.
Drugs mainly ionized at pH 7.4				
5-Sulfosalicylic acid	22	(strong)	0	<0.0001
N-Methylnicotinamide	<10	(strong)	0	0.0005 ± 0.000
5-Nitrosalicylic acid	42	2.3	0.001	0.001 ± 0.000
Salicylic acid	40	3.0	0.004	0.006 ± 0.000
Mecamylamine	20	11.2	0.016	0.021 ± 0.001
Quinine	76	8.4	9.09	0.078 ± 0.006
Drugs mainly un-ionized at pH 7.4				
Barbital	<2	7.5	55.7	0.026 ± 0.002
Thiopental	75	7.6	61.3	0.50 ± 0.05
Pentobarbital	40	8.1	83.4	0.17 ± 0.01
Aminopyrine	20	5.0	99.6	0.25 ± 0.020
Aniline	15	4.6	99.8	0.40 ± 0.042
Sulfaguanidine	6	>10.0[b]	>99.8	0.003 ± 0.000
Antipyrine	8	1.4	>99.9	0.12 ± 0.01
N-Acetyl-4-aminoantipyrine	<3	0.5	>99.9	0.012 ± 0.001

[a] The dissociation constant of both acids and bases is expressed as the pK_a, the negative logarithm of the acidic dissociation constant.
[b] Sulfaguanidine has a very weakly acidic group (pK_a > 10) and two very weakly basic groups (pK_a 2.75 and 0.5). Consequently, the compound is almos completely undissociated at pH 7.4.

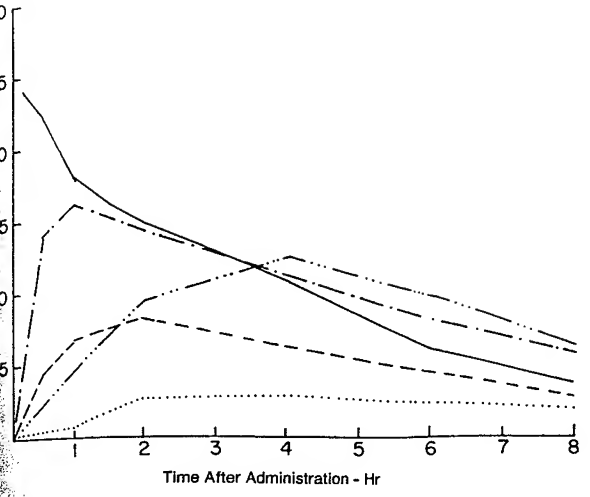

Figure 57-12. Blood concentration in mg/100 mL of theophylline (ordinate) following administration to humans of aminophylline in the amounts and by the routes indicated. Doses: per 70 kg. Theophylline-ethylenediamine by various routes:——intravenous, 0.5 g;–·–·–retention enema, 0.5 g;—• • •—• • •—oral tablets-PI, 0.5 g; - - - oral tablets-PI, 0.5 g; • • • rectal suppository, 0.5 g. (Adapted Truitt EB, et al. *J Pharmacol Exp Ther* 1950; 100:309.)

or by the alternative *lower enteral* route, through the anal portal into the rectum or lower intestine. With regard to the latter, *rectal suppositories* or *retention enemas* formerly were used quite frequently, but their popularity has abated somewhat, owing to improvements in parenteral preparations. Nevertheless, they continue to be valid and, sometimes, very important ways of administering a drug, especially in pediatrics and geriatrics. In Figure 57-12[8] the availability of a drug by retention enema may be compared with that by the intravenous and oral routes and rectal suppository administration. It is apparent that the retention enema may be a very satisfactory means of administration but that rectal suppositories may be inadequate when rapid absorption and high plasma levels are required. The illustration is not intended to lead the reader to the conclusion that a retention enema always will give more prompt and higher blood levels than the oral route, for converse findings for the same drug have been reported,[9] but rather to show that the retention enema may offer a useful substitute for the oral route.

SUBLINGUAL OR BUCCAL ROUTE—Even though an adequate plasma concentration eventually may be achievable by the oral route, it may rise much too slowly for use in some situations when a rapid response is desired. In such situations parenteral therapy usually is indicated. However, the patients with angina pectoris may get quite prompt relief from an acute attack by the *sublingual* or *buccal* administration of nitroglycerin, so that parenteral administration may be avoided. When only small amounts of drugs are required to gain access to the blood, the buccal route may be very satisfactory, providing the physicochemical prerequisites for absorption by this route are present in the drug and dosage form. Only a few drugs may be given successfully by this route.

PARENTERAL ROUTES—These routes, by definition, include any route other than the oral-GI (enteral) tract, but in common medical usage the term excludes topical administration and includes only various hypodermic routes. Parenteral administration includes the intravenous, intramuscular, and subcutaneous routes. Parenteral routes may be employed however enteral routes are contraindicated (see above) or inadequate.

The *intravenous* route may be preferred on occasion, even though a drug may be well absorbed by the oral route. There is the delay imposed by absorption before the administered drug reaches the circulation, and blood levels rise virtually as rapidly as the time necessary to empty the syringe or infusion bottle. Consequently, the intravenous route is the preferred route when an emergency calls for an immediate response.

In addition to the rapid rise in plasma concentration of drug, another advantage of intravenous administration is the greater predictability of the peak plasma concentration, which, with some drugs, can be calculated with a fair degree of precision. Smaller doses generally are required by the intravenous than by other routes, but this usually affords no advantage, inasmuch as the sterile injectable dosage form costs more than enteric preparations, and the requirements for medical or paramedical supervision of administration also may add to the cost and inconvenience.

Because of the rapidity with which drug enters the circulation, dangerous side effects to the drug may occur, which are often not extant by other routes. The principal untoward effect is a depression of cardiovascular function, which is often called *drug shock*. Consequently, some drugs must be given quite slowly to avoid vasculotoxic concentrations of drug in the plasma. Acute, serious, allergic responses also are more likely to occur by the intravenous route than by other routes.

Many drugs are too irritant to be given by the oral, intramuscular, or subcutaneous route and must, of necessity, be given intravenously. However, such drugs also may cause damage to the veins (phlebitis) or, if extravasated, cause necrosis (slough) around the injection site. Consequently, such irritant drugs may be diluted in isotonic solutions of saline, dextrose, or other media and given by slow infusion, providing that the slower rate of delivery does not negate the purpose of the administration in emergency situations.

Absorption by the *intramuscular route* is relatively fast, and this parenteral route may be used when an immediate effect is not required but a prompt effect is desirable. Intramuscular deposition also may be made of certain repository preparations, rapid absorption not being desired. Absorption from an intramuscular depot is more predictable and uniform than from a subcutaneous site.

Irritation around the injection site is a frequent accompaniment of intramuscular injection, depending upon the drug and other ingredients. Because of the dangers of accidental intravenous injection, medical supervision generally is required. Sterilization is necessary.

In *subcutaneous* administration the drug is injected into the connective tissue just below the skin. Absorption is slower than by the intramuscular route but, nevertheless, may be prompt with many drugs. Often, however, absorption by this route may be no faster than by the oral route. Therefore, when a fairly prompt response is desired with some drugs, the subcutaneous route may not offer much advantage over the oral route, unless for some reason the drug cannot be given orally.

The slower rate of absorption by the subcutaneous route is usually the reason why the route is chosen, and the drugs given by this route are usually those in which it is desired to spread the action out over a number of hours, to avoid either too intense a response, too short a response, or frequent injections. Examples of drugs given by this route are insulin and sodium heparin, neither of which is absorbed orally, and both of which should be absorbed slowly over many hours. In the treatment of asthma, epinephrine usually is given subcutaneously to avoid the dangers of rapid absorption and consequent dangerous cardiovascular effects. Many repository preparations, including tablets or pellets, are given subcutaneously. As with other parenteral routes, irritation may occur. Sterile preparations also are required. However, medical supervision is not required always and self-administration by this route is customary with certain drugs, such as insulin.

Intradermal injection, in which the drug is injected into, rather than below, the dermis, is rarely employed, except in certain diagnostic and test procedures, such as screening for allergic or local irritant responses.